

Vitamin E supplementation and macular degeneration: randomised controlled trial

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Abstract

Objective To determine whether vitamin E supplementation influences the incidence or rate of progression of age related maculopathy (AMD).

Design Prospective randomised placebo controlled clinical trial.

Setting An urban study centre in a residential area supervised by university research staff.

Participants 1193 healthy volunteers aged between 55 and 80 years; 73% completed the trial on full protocol.

Interventions Vitamin E 500 IU or placebo daily for four years.

Main outcome measures Primary outcome: development of early age related macular degeneration in retinal photographs. Other measures included alternative definitions of age related macular degeneration, progression, changes in component features, visual acuity, and visual function

Results The incidence of early age related macular degeneration (early AMD 3) was 8.6% in those receiving vitamin E versus 8.1% in those on placebo (relative risk 1.05, 95% confidence interval 0.69 to 1.61). For late disease the incidence was 0.8% versus 0.6% (1.36, 0.67 to 2.77). Further analysis showed no consistent differences in secondary outcomes.

Conclusion Daily supplement with vitamin E does not prevent the development or progression of early or later stages of age related macular degeneration.

Introduction

Age related macular degeneration (AMD) is now the leading cause of blindness and loss of vision in developed countries.^{1 2} This is due to the increased life expectancy and "greying" of the population and the successful control and treatment of other causes of blindness, such as ophthalmia neonatorum, cataract, or diabetic retinopathy. Population based studies have shown that the age specific prevalence of AMD rapidly increases in people aged over 60 years.³⁻⁵ Two thirds of people in their 90s will have AMD, and one quarter will have the most severe form (late), which is associated with serious loss of vision.²

The cause or causes of AMD are unknown, and treatment is only partially effective and appropriate in only a few.⁶ There is no effective method of prevention.

A genetic basis for AMD has been suggested,⁷ and the genes for some similar macular disorders that occur in younger people have been described.^{8 9} Associations with several measures of cardiovascular disease and its associated risk factors are inconsistent.^{10 11} Cigarette smoking is a significant risk factor for both the incidence and progression of AMD.⁴ Exposure to sunlight may contribute to its development,¹² but this association is inconsistent.^{5 13}

We undertook a prospective randomised controlled trial to examine whether a high dose supplement of vitamin E influenced the development of AMD.

Methods

Study design

This randomised trial was part of the vitamin E, cataract, and age related maculopathy trial (VECAT). Volunteers were recruited mainly through community advertising and by post between January 1995 and April 1996.¹⁴ From the 1906 people who were screened by telephone, 1289 (69%) were examined and 1204 (93%) of these were enrolled and randomised.

Annual follow up examinations were planned within one month of the anniversary of enrolment. Follow up ended in January 2000.

Randomisation

Participants randomly received either 500 IU natural vitamin E (335 mg d- α tocopherol) in a soybean oil suspension encapsulated in gelatin or a matched placebo capsule containing only the soybean oil. Vitamin E and placebo capsules were of identical appearance and taste. Neither study staff nor examiners or participants were aware of the treatment allocation, although all knew that participants would be randomly assigned to receive either vitamin E or placebo.

Outcomes

The primary outcome of the study was the development of early AMD (fig 1). Secondary outcomes were the progression of early AMD, the development of late AMD (fig 2), changes in visual acuity (the number of letters read on the LogMAR chart), and changes in visual function (VF-14 score).

Grading of age related macular degeneration

The clinical assessment of AMD was performed with 90 and 78 dioptre lenses and was graded according to

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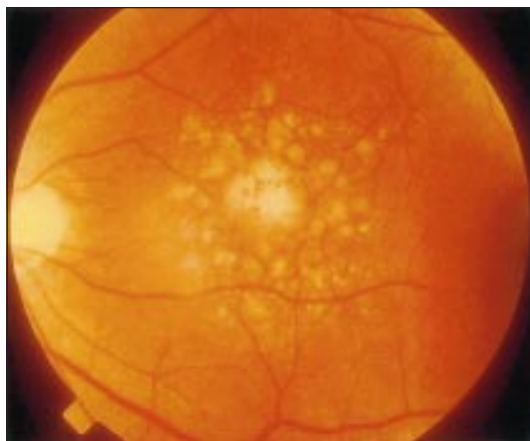


Fig 1 Early age related macular degeneration (AMD), characterised by numerous drusen of various sizes and types that extend across macular. Larger soft drusen types are of particular concern because of risk of developing into late AMD

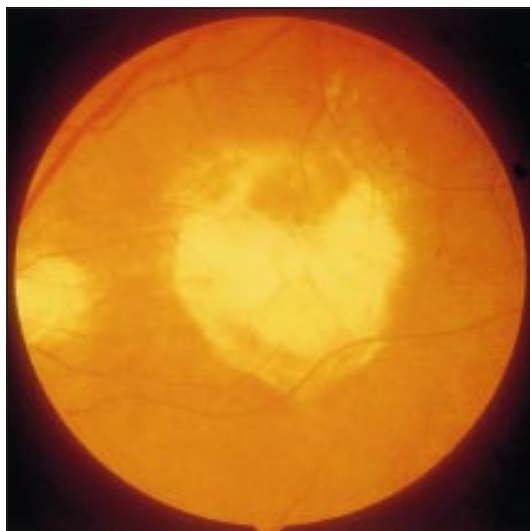


Fig 2 Late age related macular degeneration (AMD): exudative end stage. Extensive fibrovascular scar that covers macula results in severe loss of vision

the international classification.¹⁵ One frame simultaneous stereophotographs of the macula were taken and these photographs were graded independently for AMD by trained graders according to the international classification.^{15 16}

Because the international classification is somewhat ambiguous about the inclusion of soft intermedi-

ate drusen and pigmentary changes^{4 5 15} we modelled several different definitions of early AMD (table 1). Early AMD 3 was the primary outcome.

We considered that AMD progressed through six stages: (a) no drusen or only hard drusen; (b) intermediate drusen or hyperpigmentation without hypopigmentation; (c) soft drusen or pigmentary change; (d) soft drusen and pigmentary change; (e) geographic atrophy; and (f) neovascular AMD. We defined progression as movement from a lower stage to a higher stage. Participants were categorised by their worse eye.

We defined the incidence of early AMD as the appearance of early AMD in at least one eye of participants who did not have AMD in either eye at baseline. Late AMD included neovascular AMD with serious or haemorrhagic detachment of the retinal pigment epithelium or sensory retina, characteristic haemorrhages, or subretinal fibrous scars.¹⁵ We defined atrophic late AMD as a central areolar zone of retinal pigment epithelial atrophy with visible choroidal vessels, at least 175 μm in diameter, in the absence of signs of neovascular AMD in the same eye.¹⁵

Results

Characteristics of participants

We enrolled 1193 participants. The groups were highly comparable with no differences in baseline characteristics except for a small excess in the number with cortical lens opacities in the vitamin E group. The rate of compliance with the study protocol for treatment and examinations was high and similar for both groups.

Adverse events

We classified adverse events according to the body system affected. No serious adverse events were reported, though 678 people reported at least one adverse event. There was no significant difference between overall number and type of adverse event between the two groups ($\chi^2=1.82$, $df=7$, $P=0.97$).

Early AMD

Incidence—There was no difference in the four year incidence of early AMD in the two treatment groups over the four years (table 2). This was true for each definition tested and for both grading of photographs and clinical grading. Similarly, there was no difference between the incidence of the separate features of early AMD and treatment, except for hypopigmentation. Hypopigmentation was significantly less common in those on vitamin E, although the clinical significance of this is unclear. In addition, there were no differences between the groups in the prevalence of early AMD, its component features, or late AMD at baseline or at four years by either grading of photographs or clinical grading (tables 3 and 4).

Progression—According to grading of photographs 95 of 491 (19%) in the vitamin E group showed progression compared with 90 of 506 (18%) in the placebo group (relative risk=1.09, 0.84 to 1.42). By clinical grading, we observed progression in 40 of 508 (7.9%) in the vitamin E group and 31 of 514 (6.0%) in the those placebo group (1.31, 0.83 to 2.07). We saw no difference in the rate of progression of drusen types by treatment group (hard drusen being replaced by soft drusen, intermediate soft drusen being replaced by soft distinct or

Table 1 Definitions used to model early age related macular degeneration

Feature	Grading of photographs	Clinical grading
Early AMD 1	Soft intermediate or soft distinct or soft indistinct or pigment changes (hyperpigmentation or hypopigmentation)	Not applicable
Early AMD 2	Soft intermediate or soft distinct or soft indistinct and pigment changes (hyperpigmentation or hypopigmentation)	Not applicable
Early AMD 3*	Soft distinct or soft indistinct or pigment changes (hyperpigmentation or hypopigmentation)	Large/soft drusen or non-geographical RPE atrophy
Early AMD 4	Soft distinct or soft indistinct and pigment changes (hyperpigmentation or hypopigmentation)	Large/soft drusen and non-geographical RPE atrophy

RPE=retinal pigment epithelium.

*Primary outcome.

Table 2 Four year incidence* of features related to early AMD, AMD, and late AMD. Figures are numbers (percentage) of participants with feature and risk ratios (95% confidence interval)

	Grading of photographs			Clinical grading		
	Vitamin E	Placebo	Risk ratio (95% CI)	Vitamin E	Placebo	Risk ratio (95% CI)
Soft intermediate drusen	78/403 (19)	73/397 (18)	1.05 (0.80 to 1.39)	NA	NA	NA
Soft distinct drusen	29/482 (6)	28/487 (6)	1.05 (0.60 to 1.82)	NA	NA	NA
Soft indistinct drusen	7/451 (2)	7/466 (2)	1.03 (0.77 to 1.38)	NA	NA	NA
Hypopigmentation	6/470 (1)	16/481 (3)	0.38 (1.16 to 0.93)	NA	NA	NA
Hyperpigmentation	21/459 (5)	32/470 (7)	0.68 (0.41 to 1.14)	NA	NA	NA
Early AMD 1	79/339 (23)	70/330 (21)	1.10 (0.82 to 1.47)	NA	NA	NA
Early AMD 2	10/480 (2)	14/489 (3)	0.73 (0.33 to 1.62)	NA	NA	NA
Early AMD 3†	35/409 (9)	34/418 (8)	1.05 (0.69 to 1.61)	28/387 (7)	25/386 (7)	1.12 (0.66 to 1.90)
Early AMD 4	6/488 (1)	9/498 (2)	0.68 (0.25 to 1.88)	9/495 (1)	5/495 (1)	0.56 (0.20 to 1.64)
Late AMD	4/494 (1)	3/504 (1)	1.36 (0.67 to 2.77)	3/507 (1)	3/510 (1)	1.00 (NA)

NA=Not applicable to clinical grading.

*Incidence=absence of particular lesion at baseline and presence of this lesion in at least one eye at four years.

†Primary outcome.

Table 3 Prevalence of early and late AMD assessed by photograph grading at baseline and at four years. Figures are numbers (percentage) of participants

	Baseline				Four years			
	Vitamin E	Placebo	χ^2 (df=1)	P value	Vitamin E	Placebo	χ^2 (df=1)	P value
Early AMD 1	192/587 (33)	205/593 (35)	0.46	0.50	167/504 (33)	155/512 (30)	0.96	0.33
Early AMD 2	20/587 (3)	24/593 (4)	0.38	0.56	14/504 (3)	22/512 (4)	1.72	0.19
Early AMD 3	104/587 (18)	111/593 (19)	0.20	0.66	87/504 (17)	88/512 (17)	0.01	0.98
Early AMD 4	11/587 (2)	11/593 (2)	0.06	0.98	7/504 (1)	10/512 (2)	0.49	0.48
Late AMD	3/587 (0)	4/593 (1)	NA	1.00*	5/504 (1)	4/512 (1)	NA	0.75*

NA=not applicable.

*Fisher's exact test.

Table 4 Prevalence of early and late AMD as assessed by clinical grading at baseline and at four years. Figures are numbers (percentage) of participants

	Baseline				Four years			
	Vitamin E	Placebo	χ^2 (df=1)	P value	Vitamin E	Placebo	χ^2 (df=1)	P value
Early AMD 3	151/595 (25)	149/598 (25)	0.03	0.85	104/508 (21)	95/514 (19)	0.65	0.42
Early AMD 4	19/595 (3)	18/598 (3)	0.03	0.86	14/508 (3)	14/514 (3)	0.01	0.98
Late AMD	3/508 (1)	4/593 (1)	NA	1.00*	4/508 (1)	4/514 (1)	NA	1.00*

NA=not applicable.

*Fisher's exact test.

indistinct drusen, or the increase in area of either soft distinct or soft indistinct drusen; data not shown).

A masked "side by side" comparison of photographs from baseline and at four years showed no significant difference between the two groups. There was slightly more progression in the vitamin E group, which was only marginally significant (1.26, 1.01 to 1.57).

Discussion

In this four year study of the effect of vitamin E supplementation of the development and progression of early age related macular degeneration (early AMD 3) we found no protective or deleterious effect of the daily dietary supplementation of 500 IU vitamin E on incidence or progression. Further analysis of the incidence of individual features of early AMD also showed no protective effect of supplementation except for a decrease in retinal hypopigmentation and a slight increase in "side by side" progression. However, the clinical significance of these finding is unclear and may be due to chance alone. The secondary analyses of visual acuity and visual function also failed to show an intervention effect.

To our knowledge this is the first prospective randomised controlled trial to evaluate vitamin E supplementation and age related macular degeneration.

The strengths of this study include the sample size, the high rates of compliance and follow up, the prospective and randomised design, and photographic documentation. Weaknesses in the study were the relatively short follow up (four years) and the relatively low proportion of cigarette smokers.

The physicians health study showed that physicians who used either vitamin E or multivitamins had a 13% and 10% reduction in the risk of AMD respectively, although this finding was not significant.¹⁷ Since we completed our study results from the age related eye disease study (AREDS) have become available.¹⁸ That study examined the effect of a combination of antioxidants (vitamin C 500 mg/day; vitamin E 400 IU/day; β carotene 15 mg/day) with and without zinc (80 mg as zinc oxide and copper and 2 mg as cupric oxide). They found a reduction in the progression of photographic signs of AMD but only in those with moderately advanced disease in both eyes. They found no effect on earlier or later stages of AMD or in those with unilateral disease. They did not examine the effect of vitamin E supplementation on its own.

Implications

The lack of a protective effect of vitamin E supplementation is somewhat disappointing. Possibly our follow up period was too short and vitamin E may need to be

What is already known on this topic

Age related macular degeneration is the leading cause of loss of vision and blindness in elderly people; for people aged ≥ 90 years, two out of every three will be affected and one in four will become blind

Currently, there are no methods of prevention or treatment in most cases, though a third of cases are due to cigarette smoking

Antioxidant vitamins have been suggested as a possible prevention

What this study adds

Daily supplementation with 500 mg vitamin E for four years did not alter the incidence or progression of AMD

taken for a long time, if not for the whole of life, or in combination with other antioxidants. There may be a long time lag between the time of damage and the appearance of clinical signs. In addition, antioxidants may be effective only in certain subgroups of people who are at particular risk or who have a high exposure to retinal damage or oxidation, such as those with a genetic susceptibility, cigarette smokers, or those with a high ocular light exposure.¹⁹ Alternatively, our findings may mean that vitamin E does not have an important role in protecting against macular degeneration. This last conclusion would be consistent with the variable and often contradictory results obtained from previous cross sectional studies.

Contributors: See bmj.com

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Some patients shouldn't change your practice

He was covered in mud and cradling his injured wrist but clearly thought that winning the final was well worth a fractured scaphoid. "Plaster," I said, "for six weeks if you're lucky, longer if you're not."

The plaster room was in use and wouldn't be free for at least half an hour. I returned to the young man, and his noticeably cleaner supporters. They had brought his bag—good, we could use the 30 minutes to get the lad a shower. Much better to get the mud off before the plaster went on, and the bathroom was hardly ever used.

"Thank you," said the patient and his coach.

"No," said the nurses. "Last time we offered someone a bath they complained, so now we aren't allowed to do it."

Well, I'd already offered, the facility was there, and the patient was keen to get the shower he'd missed by coming to the emergency department. Meanwhile, he was a safety hazard, skittering around in studded boots, which he couldn't get off until he'd been hosed down to make the laces visible. He was wet, uncomfortable, and lived on the far side of the city.

"No," said the nurses.

Eventually, the opposition coach, who lived locally, invited the injured player home and brought him back clean.

Over-responding to complaints can be as damaging to performance and to patient care as ignoring them. We miss a lot of domestic violence. Is this because we fear complaints if we insist on separating patient and partner so that we can ask about it?

We don't always ask about or record alcohol, tobacco, and drug intake. Perhaps we don't know that these things are important, perhaps we don't care. Perhaps a patient responded to a routine query by complaining of being called a drug addict or an alcoholic, and we don't want to go through a complaints procedure again.

We accept the concept of "outliers" when we evaluate patient care. Some patient complaints are from outliers. They do not truly reflect community values or feelings, and responding to them by changing practice is unfair to other patients.

My muddy patient was 15 years ago, when I was a registrar. I haven't forgotten him, and I still offer a shower if I think it will make a patient more comfortable.

Diane Campbell *emergency physician, Alice Springs Hospital, Northern Territory, Australia*